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Mefloquine antimalarial prophylaxis in pregnancy: dose finding and pharmacokinetic study

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1 A dose finding pharmacokinetic study was performed in 20 Karen women in the third trimester of pregnancy receiving antimalarial prophylaxis with mefloquine. Ten received 250 mg mefloquine base weekly and ten received identical tablets of 125 mg base/week.

2 Both dose regimens were well tolerated. Malaria was prevented effectively, there were no serious adverse effects, all pregnancies proceeded normally, and there were no abnormalities in the babies followed up to 2 years.

3 The median time from dose administration to peak whole blood mefloquine concentration was 6 (range 3–24) h. Mean (± s.d.) peak and trough concentrations in the seventh week were 722 ± 279 and 488 ± 155 ng ml^{-1} with the 250 mg/week dose, and 390 ± 81 and 185 ± 53 ng ml^{-1} with the 125 mg/week dose regimens respectively. These blood concentration values are lower than those reported previously in non-pregnant adults.

4 One and two compartmental models were fitted to the whole blood concentration-time data. Mean (± s.d.) clearance (CL/*F*) was 0.78 ± 0.27 ml min^{-1} kg^{-1}, and the apparent terminal elimination half-life ($t_{½}$) was 11.6 ± 7.9 days.

5 Further studies to determine the oral bioavailability of mefloquine are needed, but these results suggest that clearance may be increased in late pregnancy. These preliminary results of good efficacy without significant toxicity are encouraging, and a more extensive evaluation of mefloquine antimalarial prophylaxis in pregnancy is now warranted.

Keywords mefloquine antimalarial prophylaxis pregnancy pharmacokinetics

Introduction

Falciparum malaria in pregnancy has been associated with low birth weight in areas of stable endemicity, and maternal and fetal death in areas of unstable endemicity (McGregor, 1984; WHO, 1986). It is therefore recommended that pregnant women at risk from malaria should take effective antimalarial prophylaxis (WHO, 1986). Multi-drug resistant *P. falciparum* infections pose a particular problem as there is no reliably safe and effective alternative antimalarial drug for use in pregnancy. Mefloquine, a recently introduced quinoline-methanol antimalarial, is highly effective both in the prophylaxis and treatment of chloroquine and quinine resistant falciparum malaria. In preclinical animal testing it has proved relatively safe in pregnancy compared with the other available quinoline antimalarial drugs. We report a preliminary pharmacokinetic evaluation of the drug in a group of pregnant women at high risk from falciparum malaria living on the Thai–Burmese border (Nosten *et al.*, 1987).

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Methods

Subjects

Women were enrolled into the study if they were at the beginning of the third trimester of hitherto uncomplicated pregnancy, they gave fully informed consent and agreed to regular attendance at weekly antenatal clinics conducted by one of the investigators (FN). The women were all of the Karen ethnic minority group and lived in three camps for displaced persons sited in hilly malarious terrain on the Thai–Burmese border (Nosten *et al.*, 1987). This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

Antenatal clinic procedures

Before entry to the study a detailed explanation of potential risks and benefits was given to each woman. On entry, weight and height were recorded, a full physical and obstetric assessment was made, and blood was sampled for routine haematological and biochemical tests, malaria parasite counts and baseline antimalarial drug concentrations. Stools were checked for ova and parasites. A twelve lead electrocardiogram was recorded. Women were randomly allocated in pairs to receive identical tablets of either mefloquine (base) 125 mg or 250 mg weekly (Hoffman-La Roche). Before drug administration a symptom questionnaire was recorded. Thereafter the obstetric assessment, symptom questionnaire, measurement of whole blood mefloquine concentrations and supervised administration of mefloquine was performed weekly, and electrocardiograms, haematological and biochemical tests were taken fortnightly until term. During the seventh week of the study, blood samples were taken before, then at 1, 2, 3, 4, 6, 8 h and then on days 2, 3, 4, 6 and 8 (i.e. immediately before the next dose) in order to determine peak and trough mefloquine concentrations accurately. Following delivery the newborn was weighed and examined clinically.

Mefloquine assay

In earlier studies (Franssen *et al.*, 1989; Karbwang *et al.*, 1987), we and others have found whole blood and plasma concentrations to be similar, and because there were no facilities for plasma separation at the study site, whole blood samples were taken in the present study.

Blood samples (1 ml) containing WR 184806; ± 2, 8 bis (trifluoromethyl) 4-[1-hydroxy-3-(*N*-tertbutylamino) propyl] quinoline) phosphate (400 ng) (kindly provided by the Walter Reed Army Institute of Research, Washington DC, USA) as an internal standard were added to 1 ml of acetonitrile. This was vortex mixed for 30 s and then centrifuged at 1000 *g* for 5 min. The acetonitrile phase was transferred to clean glass tubes containing 2 ml glycine buffer (0.1 M pH 9.2). This was vortex mixed for 15 s. The mixture was then extracted with 6 ml of dichloromethane and the solvent was evaporated under nitrogen. 20 μl of the methanol extract was then injected onto a Partisil/ODSIII (10 μ particle size) column (20 × 0.46 cm). The mobile phase consisted of methanol : water (70 : 30 v/v) containing octane sulphonic acid as an ion-pair reagent. The flow rate was 1.5 ml min^{-1} with u.v. detection at 222 nm. Standard curves were prepared by adding known quantities of mefloquine (50–1000 ng) to whole blood containing internal standard (400 ng). The assay limit of detection in whole blood was 20 ng ml^{-1}. The interassay coefficient of variation for spiked blood samples was 4.1% at 100 ng ml^{-1} and 5.7% at 600 ng ml^{-1}

Pharmacokinetic analysis

The accumulation in whole blood concentrations with time was analysed using an iterative least squares curve fitting programme; PC NONLIN (Metzler & Weiner, 1984). Multiple dosing programmes were used to fit mono- and bi-exponential disposition functions with first-order absorption to the unweighted whole blood drug concentration-time data. The model estimates were derived from all of the whole blood drug concentration data (i.e. both accumulation and frequent sampling profiles). The final choice of model was based on Akaike's information criterion (Akaike, 1976). Standard phrmacokinetic parameters were generated. These had the general form.

$$C_b = C^* [e^{-kt} - e^{-kat}] \quad (1)$$

$$C_b = -(C_1 + C_2)e^{-kat} + C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (2)$$

where C_b = whole blood drug concentration, ka = first order absorption rate constant, k = first order elimination rate constant, and t = time since drug administration. In equation 2, C_1, C_2, λ_1 and λ_2 are the hybrid intercept terms and rate constants, respectively. C, C_1 and C_2 are coefficient terms and λ_1 and λ_2 are fast and slow disposition rate constants. Oral clearance (CL/*F*) was calculated from the ratio; Dose/AUC.

Table 1 Clinical details

	Mefloquine dose			
	125 mg/week		*250 mg/week*	
	Mean	*s.d.*	*Mean*	*s.d.*
Age	25.8	3.6	28.1	5.0
Weight (kg)	53.6	4.0	55.2	5.7
Height (cm)	151	5.4	150	4.9
Parity	3 (range 1–7)		2 (range 1–7)	
Estimated gestation (weeks)	25.7	1.4	26.3	0.9
Weeks to delivery	10.6	4.2	9.5	2.8
Admission haematocrit (%)	30.9	5.6	30.8	4.8
Minimum haematocrit (%)	26.7	2.5	27.7	4.3

Table 2 Postnatal development (mean ± s.d. values)

Baby	*Dose/week*	*Birth*	*3 months*	*6 months*
Weight (kg)	125 mg	3.4 (0.5)	5.7 (0.5)	6.6 (0.4)
	250 mg	3.2 (0.5)	5.8 (0.8)	6.7 (0.8)
Length (cm)	125 mg	50.5 (1.2)	58.4 (2.3)	63.8 (2.2)
	250 mg	50.3 (0.9)	56.0 (2.8)	63.0 (3.0)
Head circumference (cm)	125 mg	33.4 (0.5)	39.2 (1.2)	42.0 (0.9)
	250 mg	32.2 (1.8)	39.5 (1.6)	41.6 (1.8)
Arm circumference (cm)	125 mg	9.4 (0.6)	12.5 (0.9)	13.2 (0.9)
	250 mg	9.5 (0.5)	13.4 (2.2)	13.6 (1.3)

Statistical analysis

Normally distributed data were compared using Student's *t*-test and the Mann Whitney U test was used to compare data not conforming to a normal distribution.

Results

Twenty women were studied aged between 20 and 35 years and weighing, on admission to the study, between 48 and 60 kg. The clinical and obstetric details of the two groups proved comparable and these are summarised in Table 1. There were no significant differences between the two groups. There were no biochemical abnormalities on entry to the study and none developed (with the exception of a predictable rise in serum alkaline phosphatase). A single ring form of *P. falciparum* was seen in the thick smear taken from one of the women in the 125 mg/week group in the fourth week of study. The trough whole mefloquine concentration was 156 ng ml^{-1} at this time. Another woman developed fever following a blood transfusion, which was subsequently shown to be positive for *P. falciparum*. Prophylaxis was continued in these cases. Weekly blood smears for malaria parasites were otherwise negative throughout the study.

Admission systolic and diastolic blood pressures were similar in the two groups and the mean (± s.d.) increases in systolic pressure (11.0 ± 9.9; 250 mg, 17 ± 10.6 mm Hg; 125 mg) and diastolic pressure (10.0 ± 9.4; 250 mg, 18.0 ± 6.3 mm Hg; 125 mg) were not significantly different. There were no electrocardiographic abnormalities and no significant alterations in ECG intervals. Obstetric progress was normal in both groups. There were no complications of labour and all deliveries were normal. Birthweights and post natal development were also similar in the two groups (Table 2), and development has continued normally until now, i.e. up to 2 years of age.

Toxicity

Mefloquine was well tolerated by both groups. Dizziness was reported in 14 of the women (seven in each group). There was a total of 27 reports. Dizziness was usually shortlasting and was never serious. Abdominal discomfort was noted by nine patients (3 in 125 mg/week and six in the 250 mg/week groups) and two patients in

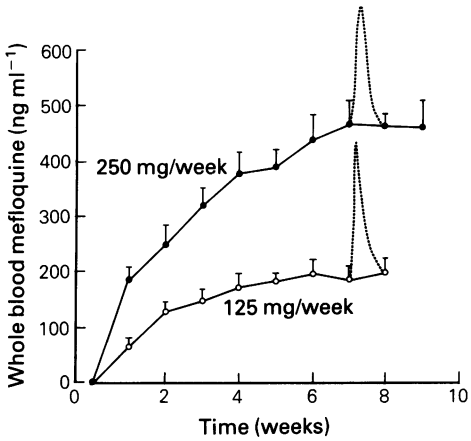

Figure 1 Mean (± s.e. mean) whole blood mefloquine concentrations ($n \geq 7$). Dotted lines represent the mean profiles during the week of intensive sampling.

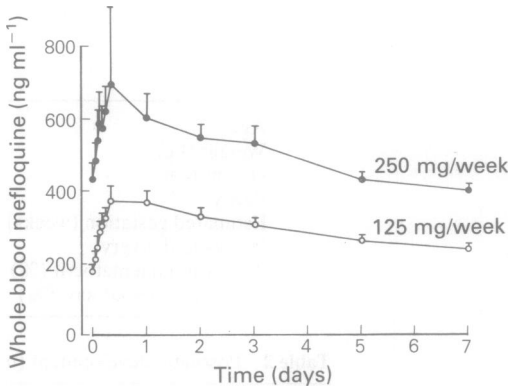

Figure 2 Mean (± s.e. mean) whole blood mefloquine concentrations during the week of intensive sampling.

the 250 mg/week group complained of diarrhoea (which was short-lived).

None of the side effects was severe or dose limiting and none of the women left the study before delivery.

Pharmacokinetics

The profiles of whole blood drug concentrations for the two dose regimens are shown in Figures 1 and 2. The overall within subject coefficient of variation for trough mefloquine concentrations after 7 weeks dosing was 16.4 ± 4.5% (mean ± s.d.). Frequent sampling was performed in 16 of the 20 women. The median time to peak mefloquine concentration was 6 h (range 3–24) and mean (± s.d.) peak concentrations were 722 (279) ng ml^{-1} with the 250 mg dose and 390 (86) ng ml^{-1} following the 125 mg dose. Equations (1) and (2) could be fitted to 17 and 16 of the data sets respectively, and on the basis of Akaike's information criterion (Akaike, 1976) equation (1) was preferable for eleven, and equation (2) for six. The areas under the whole blood drug concentration-time (AUC) curves were computed for a single dose and in the 125 mg/week group were a mean of 57% of the values in the 250 mg/week group (2251 ± 256 compared with 3955 ± 1214 ng ml^{-1} days). Thus there was no evidence of dose dependent pharmacokinetics with these regimens, and the data from the two groups were pooled. Oval clearance (CL/*F*) derived from dose/AUC values from the best fit model was 0.78 ± 0.27 ml min^{-1} kg^{-1} (mean ± s.d.; n = 17). The derived pharmacokinetic parameters for the best fit model in the individual subjects are shown in Table 3.

Discussion

In this preliminary dose finding study in pregnancy, mefloquine antimalarial prophylaxis was effective and well tolerated at both dose levels. In order to derive some estimates of the pharmacokinetic properties of the drug in late pregnancy from the accumulation in whole blood drug concentrations, no loading dose was given. The pharmacokinetic parameters derived from these data must be treated with caution for two reasons. First, women in late pregnancy cannot be considered to be at 'steady state', indeed physiological changes in late pregnancy probably happen with rate constants which are faster than those describing the terminal phase of mefloquine elimination. As a consequence there may be errors in the model derived estimates of this phase. Second, the oral bioavailability of the drug may change towards term with consequent reduction in blood concentrations. This cannot be distinguished from expansion in the apparent volume of distribution and increased clearance. Finally, some of the women delivered within 8 weeks of starting the study, thereby providing relatively few trough blood drug concentrations. These women may have been some weeks away from 'plateau blood concentrations'. Nevertheless, whole blood mefloquine concentrations in this study were lower (approximately 70%) than plasma concentrations reported in previous multiple dose studies in non-pregnant adults (Mimica *et al.*, 1983; Schwartz *et al.*, 1987). Whole blood mefloquine concentrations have been reported as between double (Schwartz *et al.*, 1982) and approximately equal to plasma concentrations (Karbwang *et al.*, 1987).

Table 3 Pharmacokinetic parameters

Patient	*Dose (mg)*	*Weight (kg)*	*Highest C_{min} (ng ml^{-1})*	*CL/F (l day^{-1} kg^{-1})*	$t_{1/2l}$ *(days)*	$t_{1/2}$ *(days)*
1	250	61	356	1.36		10.7
2	250	48	499	1.06	0.1	26.7
3	250	55	511	1.17	0.3	15.0
4*	250	60	399	1.31		8.6
5	250	56	720	0.92		21.8
6	250	49	823	0.80	3.3	22.8
7	250	48	369	2.14		4.2
8	250	53	665	1.28		8.0
9	250	59	468	1.14	3.1	17.0
10	125	46	110	1.72		6.2
11	125	58	181	1.13		11.0
12	125	55	268	0.88	0.1	25.4
13	125	51	254	1.03	0.3	4.5
14	125	59	193	0.96		3.3
15	125	51	293	1.13		6.8
16	125	52	205	1.18		6.0
17	125	54	351	0.90		5.7
18*	125	58	249	0.94		4.4
Mean		54.1		1.17	1.2	11.6
s.d.		4.6		0.33	1.6	7.9

Highest C_{min} refers to the highest trough whole blood mefloquine concentration recorded.
* Akaike Information Criterion favoured 2 compartment fit but 1 compartment data shown because of significant reversal of inter-compartmental rate constants.

There have been 14 previous studies of the pharmacokinetic properties of mefloquine in healthy adults (Desjardins *et al.*, 1979; De Souza *et al.*, 1987; Franssen *et al.*, 1989; Juma & Ogeto, 1989; Karbwang *et al.*, 1987, 1988, 1990; Looareesuwan *et al.*, 1987; Mansor *et al.*, 1989; Mimica *et al.*, 1983; Riviere *et al.*, 1985; Schwartz *et al.*, 1982, 1987). The mefloquine formulation in the original study of Desjardins *et al.* (1979) was less well absorbed than the currently available preparations (Lariam: Hoffman La Roche, and Fansimef, a combination with pyrimethamine and sulphadoxine: Hoffman La Roche). Otherwise with the exception of the study by Riviere *et al.* (1985), the reported mean estimates of oral clearance (CL/*F*) have all been lower than those in the present study; median 0.48 ml min^{-1} kg^{-1} compared with 0.78 ± 0.27 ml min^{-1} kg^{-1} (mean ± s.d.). Thus if oral bioavailability is not reduced, then elimination of mefloquine is increased in late pregnancy. Estimates of the terminal elimination half-life in the present study (mean 11.6 ± 7.9 days) are shorter than those reported previously (median 17; range 13.8–27.5 days) and are similar to those reported in malaria (Karbwang *et al.*, 1989; Looareesuwan *et al.*, 1987). However, these estimates are very dependent on the model fitted to the data. The terminal elimination half-life of quinine, which is structurally related to mefloquine, is also shortened in pregnancy (White, 1985). These results may be compared with those from six healthy Thai women taking oral contraceptives (500 μg norgestrel and 50 μg of ethinyloestradiol daily) who were given 750 mg mefloquine. Oral clearance was 0.43 ± 0.15 ml kg^{-1} min^{-1} and the terminal elimination half-life was 17.8 ± 2.8 days (Karbwang *et al.*, 1988).

In this study whole blood drug concentrations were measured, whereas in the majority of the previous reports plasma concentrations are quoted. Schwartz *et al.* (1982) found whole blood drug concentrations to be approximately double those in plasma, whereas, using a different assay method, we and others (Franssen *et al.*, 1989; Karbwang *et al.*, 1987) have found that whole blood and plasma drug concentrations are similar. Obviously if whole blood concentrations were higher, then the pharmacokinetic differences between women in late pregnancy and non-pregnant adults detailed in this study would be even larger.

The absorption of drugs may be delayed and

reduced in late pregnancy because of alterations in gut motility. There was no evidence of delayed absorption in the present study. However, absolute bioavailability and therefore completeness of absorption cannot be determined. The rate of mefloquine absorption was comparable with that observed in other studies with the current formulation. Times to peak concentration ranged from 3–24 (median 6) h which compares with previously reported mean values of 5.7–20.7 (median 14) h. Mean peak mefloquine concentration in the 250 mg/week group was 722 $\mu g\, l^{-1}$ which is significantly lower than the mean value of 1387 $\mu g\, l^{-1}$ recorded in six healthy adult Brazilian volunteers, 12 h after taking their 21st weekly dose of 250 mg (Schwartz *et al.*, 1987). The mean peak to trough difference was also approximately half in the present study; 275 compared with 520 $\mu g\, l^{-1}$.

These data suggest that there are potentially important differences between the pharmacokinetic properties of mefloquine in pregnant and non-pregnant adults. As a result blood mefloquine concentrations for a given dose are lower. Increased clearance has been documented for many drugs in late pregnancy, often accompanied by an expansion in the volume of distribution. Several factors are thought responsible including increased plasma volume, body water and fat, altered protein binding, and increased glomerular filtration rate. In non-pregnant adults mefloquine is highly protein bound (> 98%) in plasma, and changes in binding in pregnancy might account for some of these alterations in pharmacokinetic properties. These data on mefloquine blood concentrations in pregnancy provide a framework for choosing prophylactic dose regimens. The clinical and obstetric results of this preliminary investigation are encouraging. The efficacy and toxicity of mefloquine prophylaxis in pregnancy should now be evaluated in larger prospective studies.

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